

Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested. By the present amendment claims 1 and 42 have been amended. Since the present amendments do not add new matter or require further searching by the Examiner, it is believed that the present amendments are appropriate.

1. 35 U.S.C. § 112 rejection of claim 42

Claim 42 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that the recitation of two identical membranes is not supported by the originally filed specification.

Claim 42 has been amended to recite two membranes that have substantially identical gas permeability to more clearly define the present invention. As stated on page 11, lines 26-30 of the originally filed specification, the gas permeable membranes 22 and 24 may for example, be a fluoro-ethylene-propylene (FEP) membrane. The gas permeability of FEP for biologically relevant gases is nominally 1.6×10^3 and $25.9 \times 10^3 \text{ cm}^3/\text{m}^2\text{-day-atm}$ for O_2 and CO_2 , respectively, across a 0.026 mm film at 25°C . Since two membranes constructed of the same material necessarily have substantially identical gas permeability, the amended subject matter is supported by the originally filed specification. Accordingly, it is respectfully submitted that the rejection of claim 42 has been overcome. Since the present amendment to claim 42 merely clarifies the subject matter of the invention, the amendment is believed to be appropriate.

2. 35 U.S.C. §102(b) rejection of claims 1-9, 12, and 14

Claims 1-9, 12, and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by Vetillard (WO 0206441). It is respectfully submitted that amended claim 1 is patentable over Vetillard and is therefore allowable.

Amended claim 1 recites a bioreactor including a housing defining a first chamber that contains a first liquid medium. At least one gas permeable membrane defines at least a portion of the housing. The membrane allows gas flow through the housing into the first chamber. A hydrostatic loading module transmits hydrostatic pressure through the membrane to the first liquid medium contained in the first chamber.

Anticipation requires a single prior art reference that discloses each element of the claim. W. L. Gore & Associates v. Garlock, Inc., 220 UPSQ 303, 313 (Fed. Cir. 1983) *cert. denied* 469 U.S. 851 (1984). For a reference to anticipate a claim, “[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.” Scripps Clinic & Research Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

The Examiner asserts that reciting a loading module for transmitting hydrostatic pressure constitutes a recitation of intended use and, thus, the prior art need only *be capable of* performing the intended use to anticipate the claimed subject matter (Office Action page 9). As amended, however, claim 1 requires a hydrostatic loading module that not only is capable of transmitting hydrostatic pressure through a membrane, but a loading module *that actually transmits*

hydrostatic pressure through the membrane. Vetillard does not teach or suggest such a loading module.

The Examiner asserts that zones C1 and C3 constitute hydrostatic loading modules and that the “downward phase” and “ascending phase” are created by varying pressure within the hydrostatic loading modules (Office Action page 3). In Vetillard, however, these phases are always conducted under hydrodynamic conditions – not hydrostatic. In particular, Vetillard teaches that, during the downward phase, the pump P1 continually circulates nutritive media F1 from the vessel R1, through the zone C1, and back into the vessel (Fig. 2 and Fig. 6). In other words, the nutritive media F1 is not constrained or otherwise held static within the zone C1 at any time. Accordingly, the nutritive media F1 is constantly moving through the zone C1 and thereby applies hydrodynamic pressure p_1 through the membrane M1 and into the zone C2. The pressure p_1 forces waste products to drain from the zone C2, through the membrane M3, into the zone C3, and out of the system via a valve V3 (Fig. 2). This drainage is accomplished while the pump P3 is inactive, i.e., when no fluid is supplied to the zone C3 and, thus, no pressures of any kind are exerted from the zone C3 towards the membrane M3 during the descending phase. Therefore, the only forces present during the downward phase are hydrodynamic forces.

Likewise, during the ascending phase, the pump P3 circulates dynamic liquid media F3 from the tank R3, through the zone C3, and into the waste disposal tank (Fig. 6). In other words, the liquid media F3 is not constrained or otherwise held static within the zone C3 at any time. Accordingly, the liquid media F3 is constantly

moving and applies hydrodynamic pressure p_3 through the membrane M3 and into the zone C2, thereby causing nutrients in the media F3 to ascend through the zone C2 and into the zone C1 to replenish the tank R1 of fresh nutrient media F1 (Fig. 3). This replenishing is accomplished while the pump P1 is inactive, i.e., when no fluid is supplied to the zone C1 and, thus, no pressures of any kind are exerted from the zone C1 towards the membrane M1. Therefore, the only forces present during the ascending phase are hydrodynamic forces.

Vetillard teaches that, this inversion of flow from the zone C2 back into the zone C1 makes it possible to create trans-membrane flows subjected to low hydrodynamic stresses compatible with the fragility of the cultivated cells. Thus, a system of “laminar” slow flows is obtained (Paragraph 144 – emphasis added). Based on the foregoing, it is clear that any pressure applied through the membranes M1 or M3 is due to hydrodynamic forces. Accordingly, Vetillard does not teach or suggest a hydrostatic loading module that applies hydrostatic pressure through a membrane as recited by amended claim 1. For these reasons, it is respectfully submitted that amended claim 1 is patentable over Vetillard and therefore allowable.

Claim 2 recites that the hydrostatic loading module transmits the pressure by a static second liquid medium. As noted, Vetillard teaches a bioreactor in which both the fresh nutrient media F1 and the liquid media F3 are continually in motion while being perfused through the zones C1 and C3, respectively. Accordingly, Vetillard does not teach or suggest a hydrostatic loading module that transmits pressure by a static second liquid medium. For these reasons, it is respectfully submitted that claim 2 is patentable over Vetillard and is therefore allowable.

Claims 3-9, 12, and 14 depend from claim 1 and are allowable for at least the same reasons as claim 1 and for the specific limitations recited therein.

3. 35 U.S.C. §103(a) rejection of claims 10, 11 and 13

Claims 10, 11, and 13 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vetillard (WO 0206441) as applied to claim 1, and further in view of Jensen (US20040077075). Claims 10, 11, and 13 depend from claim 1 and are allowable for at least the same reasons as claim 1 and for the specific limitations recited therein.

4. 35 U.S.C. §103(a) rejection of claim 42

Claim 42 is rejected under 35 U.S.C. §103(a) as being unpatentable over Vetillard (WO 0206441) as applied to claim 1, and further in view of Puchinger (US 4225671). It is respectfully submitted that the combination of Vetillard and Puchinger does not teach or suggest the structure recited in amended claim 42, and modifying Vetillard to exhibit the construction recited in amended claim 42 would result in a device that is unsuitable for its intended purpose.

Amended claim 42 recites that two membranes having substantially identical gas permeability are positioned on opposite sides of the first chamber.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 35 U.S.C. § 103 forbids issuance of a patent when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains.” In making a determination of obviousness under 35 U.S.C.

§103(a):

...the scope and contents of the prior art are determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. Graham v. John Deere, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, *there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.* KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741; 2007 U.S. Lexis 4745; 167 L. Ed. 2d 705; 75 U.S.L.W. 4289 (2007) (emphasis added), *citing* In re Kahn, 441 F.3d 977, 988 (CA Fed. 2006).

Also, in KSR Int’l. Co. V. Teleflex, Inc., the U.S. Supreme Court noted that the analysis supporting a rejection under 35 U.S.C. 103(a) should be made explicit, and that it was “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed.” KSR at 1741.

In Vetillard, the membranes M1 and M3 specifically have different constructions, namely cutting thresholds of .2-.4µm and 10-12KDa, respectively (Paragraphs 41-42), in order to accomplish the dual objective of draining waste in one direction and replenishing the nutrient media tank in the other. In other words,

Vetillard teaches away from a bioreactor construction having substantially identical membranes.

The Examiner asserts that one having ordinary skill in the art would have recognized that it would have been beneficial to ensure that the Vetillard membranes were identical if both of the membranes interact with the same type of culture fluid or are intended to perform the same function (Office Action page 8). The MPEP, states that if a proposed modification would render the invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification of the invention (MPEP §2143.01, relying on *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). It is respectfully submitted that modifying the bioreactor of Vetillard as proposed would render the bioreactor of Vetillard unsatisfactory for its intended purpose and, thus, the proposed modification of Vetillard would not be obvious to one having ordinary skill.

Vetillard teaches that the dynamic liquid media F1 and F2 must be different in order for the bioreactor to properly function. In particular, Vetillard teaches that the bioreactor is designed to achieve economic optimization of the cells culture by recycling the growth factors of the media while sufficiently evacuating the cell wastes from the culture media (Paragraph 13). In other words, Vetillard states that multiple functions are performed on the cell culture by surrounding the cell culture with two different liquid media F1 and F2 and allowing the respective functions, i.e., growth factor recycling and waste removal, to be performed through two membranes M1 and M3 having different cutting thresholds. In fact, Vetillard differentiates the

membranes by designating each with the specified function each performs, namely the feeding membrane M1 and the dialysis membrane M3 (Paragraphs 41-42).

More specifically, the first liquid media F1 is specifically designed to feed the culture media in nutrient elements rich in growth factors (Paragraph 86). On the other hand, the second liquid media F2 is specifically designed to 1) introduce the cells to be cultivated into the chamber; 2) transport vectors of gene transfer and allow their setting in contact with the cells to establish a membrane fusion between the target cells and the vector of gene transfer; and 3) rinse the flow of inhibiting macromolecules present within the chamber (Paragraphs 88-89 and 92). Due to the different functions performed by the first and second liquid media F1 and F2, the membranes separating the liquid media from the cell culture must necessarily have different gas permeability, otherwise the operability and effectiveness of the bioreactor would be significantly frustrated.

If for example, the first and second membranes M1 and M3 both had a cutting threshold of $.22\mu\text{m}$, the growth hormones and large proteins provided by the first media F1 would be allowed to pass through the second membrane and into the waste disposal tank (see Figs. 4-6), thereby rendering the bioreactor incapable of replenishing the vessel R1 of fresh nutrient media during the ascending phase (Fig. 3). Therefore, the particularized functionality of the first and second liquid media F1 and F2 requires two different liquid media and therefore two membranes having different gas permeability. This is further evidenced by Vetillard repeatedly emphasizing the use of several *distinct* liquid media (*e.g.* Paragraphs 85 and 96) as well as the used of membranes having *different* cutting thresholds (*e.g.* Paragraphs

42 and 48). Accordingly, Vetillard does not teach, suggest or even contemplate using two substantially identical culture fluids or culture fluids that are intended to perform the same function as the Examiner asserts. For these reasons, one having ordinary skill would not modify Vetillard to exhibit membranes having substantially the same gas permeability as such a modification would clearly produce a device that frustrates the very objective of Vetillard.

The teachings of Puchinger do not negate the undesirable effects of modifying Vetillard to exhibit multiple membranes having substantially identical gas permeability. Regardless, Puchinger does cure the deficiencies of Vetillard. Puchinger teaches a plate membrane system in which cells 101 in a cell culture space 104 are perfused with culture medium from one or more culture medium spaces 105, 106 separated by two semi-permeable membranes 102 and 103. When only one culture medium space 106 is used, the other space 105 acts as a gas space, and the membrane 102 is gas-permeable but not water permeable (Col. 4, lines 3-5). A suitable culture medium is perfused through the culture space 106 to cultivate the cells and then a suitable gas mixture is perfused through the culture space 105. In other words, the membranes 102 and 103 do not have identical gas permeability when more than one interactive fluid, i.e., a culture medium and a subsequent gas mixture, is used to cultivate the cells.

Accordingly, it is clear that Puchinger does not teach or suggest the use of identical membranes when multi-function cultivation is performed on the cells and, thus, Puchinger does not cure the deficiencies of the multi-function bioreactor taught by Vetillard. Accordingly, it is respectfully submitted that amended claim 42 is

patentable over the combination of Vetillard and Puchinger and is therefore allowable.

In view of the foregoing, it is respectfully submitted that the present application is in a condition of allowance and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/

Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone: (216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705